REMARKS

Claims 1, 2 and 4-14 are all the claims pending in the application and have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Makovec, et al. (U.S. Patent No. 5,130,474) in view of Midler, et al. (U.S. Patent No. 5,314,506). For the following reasons, Applicants respectfully traverse this rejection.

Applicants submit that the rejection is unsupported. As it is clearly stated in the description, the object of the invention is to provide a method which can produce crystalline dexloxiglumide having flowability characteristics suitable for the formulation of a tablet (cf. page 2, third paragraph).

Midler does not deal at all with the same problem and it is directed to a crystallization process which provides for the direct production of small crystals (at least 95% with $d<25$ μm) in order to improve bioavailability and provide a short dissolution time of the active agent.

Indeed Midler is not concerned with problems arising from the tablet production and, indeed, the features of the crystals which are obtained by Midler are totally different and quite the opposite with respect to the features of the crystals which are required by the present invention for the purpose of tabletting.

The crystallization method which is claimed by the invention and fully described allows to obtain a product with crystals having a dimension (D50) between 50 and 130 μm (claim 6 and claim 1, as amended), or in the best situation with an average dimension from 80 to 100 μm (claim 7). Moreover, it is particularly important that the method of the invention, as recited in amended claim 1, provides dexloxiglumide having a "fine particle fraction", namely particles

with a diameter lower than 10 μm, in an amount lower than 15% of the total. As pointed out before, such requirements are totally in contrast with the particle size which is obtained according to Midler.

Moreover, the method of the invention provides particles with a Span index below 2.5; for the definition of the Span index, please refer to page 6, line 5; the Span index is a measure of the width of the particle size distribution; the narrower the distribution the lower is the Span index. The value of 2.5 indicates that the particle size distribution is very narrow (cf. for example figure 1A in the patent specification relating to lot PP/9282 which has a Span index of 1.608).

As presently claimed the method of the invention, in order to achieve the above-mentioned features requires the use of isopropylether as the solvent and the addition of a seeding of microcrystalline dexloxiglumide having an average particle size D50<20 μm. Midler does not even remotely suggest such features.

Moreover, as Applicants have previously argued and as has been explained by Dr. Makovec in the declaration under 37 CFR § 1.132, with the preparation of lots without adding a "seeding material" and even with the use of isopropylether as a solvent (which is not taught or suggested by any of the references of record) a product is obtained such as that exemplified by lot G3756 (which constitutes an annex to the declaration) with an average particle size D50 of 15.025 μm and a Span index of 3.85, that is having negative features similar to those obtained by means of crystallization from ethanol-water (which constitutes state of the art).

Indeed, the present invention solves problems relating to the industrial preparation of tablets. The industrial problems found when a material having the features of lot G3756-A is used in the preparation of tablets are mainly the following:

- bad free-flowing features of the powders, and

- caking phenomena during the compression process; for clarity, we point out that the term "caking" is meant to indicate physical changes undergone by the powder to be compressed, induced by pressure and heat which develop during the compression process.

Such drawbacks were so strong as to hinder the regular functioning of the tabletting apparatus. On the contrary, all the lots of dexloxiglumide prepared according to the process of the invention and having the features of claims 6-8 (the limitation of claim 6 having been added to claim 1 herein) had very good free-flowing properties and did not cause any caking phenomenon during the tablets preparation.

In summary, the method of crystallization and the resulting product which is claimed by the present application is totally different from that described by Makovec et al. (US 5,130,474) and from that described by Midler (US 5,314,506) which moreover does not relate to dexloxiglumide. The method described by Midler allowed one to obtain by means of a peculiar technique (simultaneous use of solvent and of an anti-solvent) the precipitation of different drugs, the particles of which had a dimension such that at least 95% of the particles had a diameter of 25 μm or less. Accordingly Midler aimed at obtaining crystals with a dimension which is much lower than that of the crystals obtained by the method of the invention. As stated

before Midler is not concerned with tabletting process and does not provide a solution to the problem of providing tablets by means of an industrial process.

As a conclusion, Applicants point out that the method of the invention is totally different from those described in the prior art. In fact, Makovec et al. made use of a different solvent for crystallization and obtained a powder which is not suitable for the industrial preparation of tablets, whereas Midler makes use generally of a crystallization method with the combined use of a solvent and of an anti-solvent, without indicating the use of a "seeding material" having a required particle size.

The favorable results which are obtained by the method of the invention are indeed thoroughly unexpected and could not be derived from the teaching of the prior art. Accordingly, it is submitted that all claims, including new claim 15, patentably distinguishes over the prior art.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

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Respectfully submitted,

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